



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application No.: 10/079,931  
Applicants: Kuijpers et al.  
Filed: February 19, 2002  
Title: TREATMENT OF OCULAR DISORDERS  
TC/A.U.: 1644  
Examiner: Nolan, Patrick  
Confirmation No.: 7525  
Docket No.: 294-70 CON/RCE  
Dated:

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION UNDER 37 C.F.R. § 1.132**

Sir:

I, ROBERTUS WILHELMUS KUIJPERS, M.D., Ph.D., 311 Heemraadssingel, 3023  
BR Rotterdam, declare as follows:

1. I am an expert in the field of Ophthalmic Immunology as evidenced by my resume, which is attached as Exhibit A. Additionally, I am one of the inventors of the above-identified U.S. Patent application, filed on February 19, 2002, which is a continuation application of U.S.S.N.: 09/258,240, filed February 26, 1999.

2. The action of somatostatins (*i.e.* somatostatin analogues) is biochemically different from the action of tyrosine kinase inhibitors.

3. Somatostatin analogues act directly on retinal cells. Somatostatin receptors are coupled to G proteins in the cell membrane, and generate a transmembrane signal after binding of somatostatin analogues. Depending on the cell types, somatostatin receptors are coupled to a diversity of signal transduction pathways. Various signalling proteins, including adenylate cyclase, guanylate cyclase, phospholipase C, phospholipase A2, potassium, and calcium channels, Na<sup>+</sup>/H<sup>+</sup> exchanger, Src, Erk1/2 and p38 mitogen-activated protein (MAP) kinases

and tyrosine phosphatases have been reported.

4. The action of tyrosine kinase inhibitors involves inhibition of phosphorylation and activation of effector proteins. Many polypeptide growth factors activate cells through membrane receptors with cytoplasmatic tyrosine kinase activity. The effect depends on the type of receptor and the type of tyrosine kinase that are involved. There are many types tyrosine kinases.

5. I have read and understood U.S. Patent No. 6,028,099 in the way that although all possible Tyr-kinase inhibitors with the basic chemical structure which is shown in claim 1 of the patent could be used, in fact the work has been done using the protein kinase pathway inhibitor genistein. Genistein is a phytoestrogen that can be found in soy products and binds preferentially to estrogen receptor beta. The patent is focused on protein kinase inhibitors and inhibition of neovascularization which, in my understanding, may mean vascular endothelial growth factor (VEGF)-receptor coupled tyrosine kinase inhibition.

6. Since the action of somatostatin analogues is different from the action of tyrosine kinase inhibitors, the compounds are used separately from each other. To the best of my knowledge, no cumulative action, nor synergistic action, of these two compounds has been described in the treatment of retina diseases.

7. Somatostatin analogues have been used for more than 15 years and have been proven to be safe drugs.

8. Tyrosine kinase inhibitors are not yet on the market, or only recently introduced on the market. Tyrosine kinase inhibitors have been described with a significant pattern of side-effect.

9. It is likely that when one uses two active compounds together (instead of just one active compound) more side effects may occur.

10. I believe that a somatostatin analogue administered *without* a kinase inhibitor provides a safer clinical profile than a somatostatin analogue administered *with* a kinase inhibitor.

11. In one embodiment, the instant invention includes a method for treating an ocular disorder by administering a somatostatin analogue (e.g., octreotide and lanreotide) to a patient. The somatostatin analogue binds to at least one somatostatin receptor in the eye.

12. The ocular disorders treatable by this method include retinal edema, macular edema, cystoid macular edema, age related macular degeneration, diabetic retinopathy, and central serous chorio-retinopathy.

13. Topical administration of a somatostatin analogue is effective in treating the aforementioned ocular disorders. Further experimental results will follow.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that those statements were made with the knowledge that willfully false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willfully false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: \_\_\_\_\_

\_\_\_\_\_  
Robertus Wilhelmus Kuijpers, MD

## CV.

## EXHIBIT A

Robert W.A.M. Kuijpers  
Born 20-09-1958

## Education:

MD	Rijks Universiteit Leiden	1986
PhD	"neonatal alloimmune cytopenias"	
	Universiteit van Amsterdam	1992
	Clinical training Ophthalmology	
	Academisch Ziekenhuis Maastricht	1991-1995
	Diplome European Board of ophthalmology	1995

Scientist and head of Laboratory for leukocyte serology	
Centraal Laboratorium voor de	
Bloedtransfusiedienst (CLB) and Laboratory for	
experimental immunology, Universiteit van Amsterdam	1989-1991
Staffmember University eye clinic,	
Academisch Ziekenhuis Rotterdam	from 1995

Member American Academy of Ophthalmology (AA)

Member American Organisation for Research in Visual Science and Ophthalmology (ARVO)

## Publications:

Kuijpers RWA, Faber NM, Kanhai HH, Von dem Borne AE. Typing of fetal platelet alloantigens when platelets are not available. *Lancet* 336 (8726):1319, 1990

Huizinga TW, Kuijpers RWA, Kleijer M, Schulpen TW, Cuypers HT, Roos D, Von dem Borne AE. Maternal genomic neutrophil FcRIII deficiency leading to neonatal isoimmune neutropenia. *Blood* 76 (10):1927, 1990

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Markhorst DG, Hack WW de Waal FC, Kuijpers RWA. A child with neonatal allo-immune neutropenia. *Tijdschrift voor Kindergeneeskunde*. 58 (5):175, 1990

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Kuijpers RWA, Faber NM, Cuypers HT, Ouwehand WH, Von dem Borne AE. NH2-terminal globular domain of human platelet glycoprotein Ib alpha has a methionine 145/threonine 145 amino acid polymorphism, which is associated with the HPA-2 (Ko) alloantigens. *Journal of Clinical Investigation* 89 (2):381, 1992

Kuijpers RWA, Von dem Borne AE, Kiefel V, Eckhardt CM, Waters AH, Zupanska B, Barz D, Taaning E, Termijtelen A, Ouwehand WH. Leucine33-proline33 substitution in human platelet glycoprotein IIIa determines HLA-DRw52a (Dw24) association of the immune response against HPA-1a (Zwa/PLA1) and HPA-1b (Zwb/PLA2). *Human Immunology* 34 (4):253, 1992

Dooren MC, Kuijpers RWA, Joekes EC, Huiskes F, Goldschmeding R, Overbeeke MA, Von dem Borne AE, Engelfriet CP, Ouwehand WH. Protection against immune haemolytic disease of newborn infants by maternal monocyte-reactive IgG alloantibodies (anti-HLA-DR). *Lancet* 339 (8801):1067, 1992

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Kuijpers RWA, Ouwehand WH, Peelen W, Michiels JJ, Engelfriet CP, Von dem Borne AE. Thrombocytopenia due to platelet glycoprotein IIb/IIIa reactive autoantibodies non-reactive with platelets from EDTA blood. *Vox Sanguinis* 63 (2):119, 1992

Kuijpers RWA, Simsek S, Faber NM, Goldschmeding R, Van Wermeskerken RK, Von dem Borne AE. Single point mutation in human glycoprotein IIIa is associated with a new platelet-specific alloantigen (Mo) involved in neonatal alloimmune thrombocytopenia. *Blood* 81 (1):70, 1993

Schreij G, Kuijpers RWA, Pijpers E, Beintema MR. Unusual ocular symptoms and signs associated with infectious mononucleosis. *Lancet* 344 (8932):1302, 1994

Kuijpers RWA, Van den Anker JN, Baerts W, Von dem Borne AE. A case of severe neonatal thrombocytopenia with schizencephaly associated with anti-HPA-1b and anti-HPA-2a. *British Journal of Haematology* 87 (3):576, 1994

Simsek S, Vlekke AB, Kuijpers RWA, Goldschmeding R, Von dem Borne AE. A new private platelet antigen, Gro-a, localized on glycoprotein IIIa, involved in neonatal alloimmune thrombocytopenia. *Vox sanguinis* 67 (3):302, 1994

La Heij E, Kuijpers RWA, Baarsma S, Kijlstra A, Mooij CM. Integrin expression on histological specimen of iris-biopsies in Fuchs iridocyclitis. *British Journal of Ophthalmology*, 82(4):432, 1998

Kuijpers RWA, Baarsma S, Van Hagen CM. Treatment of cystoid macular edema with octreotide. *New England Journal of Medicine*, 338 (9):624, 1998

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Kuijpers RWAM, Vingerling JR. *Zakboek oogheelkunde*. Maarsen, 1999; Elsevier / Bunge

van Hagen PM, Baarsma GS, Mooy CM, Fircoskan EM, ter Averst E, Hofland LJ, Lamberts SW, Kuijpers RW. Somatostatin and somatostatin receptors in retinal diseases. *Eur J Endocrinol* 2000 Oct;143 Suppl 1:S43-51. No abstract available.

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van Hagen PM, Mooy CM.  
Somatostatin receptor 2A expression in choroidal neovascularization secondary to  
age-related macular degeneration.  
Invest Ophthalmol Vis Sci. 2000 Jul;41(8):2329-35.